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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,986	07/24/2003	Li-Huei Tsai	10498-00054	3395

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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,986	TSAI ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-100* is/are pending in the application.

4a) Of the above claim(s) *1-72 and 86-100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-100 are pending.

Election/Restrictions

Applicant's election with traverse of Group V claims 73-84 in the reply filed on 4/21/06 is acknowledged. The traversal is on the ground(s) that the subject matter of claims 1-100 is interrelated to the extent that a search and examination of the subject matter of those claims in the same application would not be overburdensome. Most of the inventions set forth in the restriction requirement mailed Dec. 8, 2005 are in separate class and subclass. This alone establishes a search burden. In addition, the inventions are of materially different and separate subject matter so that a search of one invention is not co-extensive, for example, a search of group I, for a method of treatment, will not provide a search on a method of identifying compounds of group IV. Applicant's arguments to rejoin all recited Groups which encompass claims 1-100 is not found persuasive, however, it is found reasonable to rejoin Groups V and VI claims 73-85, because a cell derived from the claimed transgenic mouse reads on the claimed transgenic mouse.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-72, 86-100 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/21/06.

Claims 73-85 are under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 73-85 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a nucleic acid sequence encoding the human p25 operably linked to an inducible Tetracycline (Tet) Tet on/Tet off CaMKII promoter, and a second transgene comprising a DNA sequence encoding an inducer operably linked to the tissue-specific promoter, wherein p25 is expressed and wherein the mouse has neurodegenerative pathology, does not reasonably provide enablement for all tissue specific promoter Tet on/Tet off system transgenic mice that have behavioral symptoms of Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 73-84 are directed to a transgenic (Tg) mouse overexpressing in the brain or the forebrain a nucleic acid encoding p25 operably linked to an inducible Tetracycline (Tet) on/Tet off CaMKII promoter and a second transgene comprising a DNA sequence

encoding an inducer operably linked to the forebrain tissue-specific promoter. The mouse is further claimed to exhibit features of progressive neurodegeneration, tau aggregation, neurofibrillary tangle formation, aberrant cyclin-dependent kinase 5 activity, neuronal loss in the cerebral cortex, neuronal loss in the hippocampus, severe brain atrophy, reactive astrogliosis, caspase 3 activation, upregulation of C99, upregulation of beta-amyloid, tau hyperphosphorylation, amyloid precursor protein phosphorylation and amyloid precursor protein hyperphosphorylation, and other neuropathological and/or behavioral phenotypes.

Claim 85 is directed to a transgenic cell line derived from said transgenic mouse.

The specification teaches a transgenic mouse overexpressing human p25 under the Tet on/Tet off expression system in the postnatal forebrain, wherein said Tg mouse exhibits many of the biochemical and cellular aspects of AD neuropathology (specification p 64, 2nd paragraph, and p 65, 1st and 2nd paragraph). The specification has asserted the transgenic non-human animals and cells overexpressing p25 in a tissue-specific manner exhibit many of the features of human tauopathies and Alzheimer's disease (AD) in that they display progressive neurodegeneration pathology (p 4, 2nd paragraph). It is an object of the invention to use the p25 Tg non-human animals described herein as an in vivo model of human neurodegenerative disorders such as tauopathies and AD (specification p 4, 2nd paragraph last three lines). However, the specification has failed to provide guidance and/or working examples correlating to the creation of a transgenic mouse overexpressing p25 under the inducible Tet on/Tet off system wherein said Tg mouse exhibits one or more behavioral

symptoms of AD. The guidance provided by the specification does not correlate to the use of the Tg mouse and the transgenic cells as an animal model for human neurodegenerative disorders such as tauopathies and AD for the breadth of the claims. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

In determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are; the breadth of the claims, the nature of the invention, the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

These factors are analyzed, in turn, and demonstrate that one of ordinary skill in the art will need to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

As a first issue, the claims 73-84 embrace a transgenic mouse having the human p25 gene overexpressed in the brain or forebrain of the mouse under the inducible Tet on/Tet off regulatory system wherein said Tg mouse exhibits tissue specific neurodegenerative pathologies, and one or more behavioral symptoms of AD. The specification has asserted that the presence of an activity, phenotype or symptom associated with a neurodegenerative disorder (e.g., AD) may be identified from a biological sample taken from, for example, the Tg animals wherein biological samples may be from any biological tissue or fluid or cells (specification p 21, 2nd paragraph). However, the specification has failed to provide guidance and/or working examples correlating to the creation of a transgenic mouse overexpressing p25 under the inducible Tet on/Tet off system using all inducible tissue specific promoters as embraced by the claims, other than the CaMKII promoter, wherein said Tg mouse exhibits one or more behavioral symptoms of AD. The state of the transgenic animal art has set forth that phenotypes resulting from expression of a transgene are unpredictable. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. **Sigmund** also states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype

(Arterioscler Throm Vasc Biol 20: 1425-1429, 2000) (p 1426, 1st column). Even after the filing of the instant application, **Ristevski et al,** (Molecular Biotechnology, 29: 1530163, 2005) reports that common problems associated with the generation of transgenic mice include the site of integration is uncontrolled and yet is critical due to possibility of integration into a silent locus (p 159, 1st column, 2nd paragraph). **Ristevski et al,** notes tat random integration may result in the insertional inactivation (insertional mutagenesis) of a gene at the site of integration, resulting in loss of function that may be mistakenly attributed to overexpression of the transgene (p 159, 1st column, 2nd paragraph). In addition, to the problems associated with the random transgene integration, it is difficult to control transgene copy number (usually integration is singular even with multiple copies integrated in tandem) (**Ristevski et al,** p 159, 1st column, 3rd paragraph). The specification asserts that a Tg animal of the invention can be created by introducing a p25 nucleic acid into the male pronuclei of a fertilized oocyte, for example, by microinjection or retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal and methods of generating Tg animals via embryo manipulation and microinjection, have become conventional in the art (specification p 33). **Cameron et al,** (Molecular Biotechnology, 7: 253-265, 1997) noted that the process of microinjection results in a proportion of embryos being lysed at the time of injection and in animals integration into the genome has occurred beyond the one-cell stage, resulting in mosaicism (p 255, 1st column). While the intent is not to say that the transgenic mouse of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are unpredictable. Given the

unpredictability in the expression of a transgene, in the instant case the expression of the p25 gene under the inducible Tet on/Tet off system resulting in one or more behavioral symptoms of AD, particularly when taken with the lack of guidance and/or working examples in the specification correlating to said transgenic mouse whose genome comprises said transgene resulting to one or more behavioral symptoms of AD, it would have required undue experimentation to predict the results achieved in a mouse comprising and expressing instant gene and the consequences of that product, and therefore, the resulting behavioral phenotype(s).

As a second issue, the claims are directed to a transgenic mouse overexpressing in the brain or forebrain a nucleic acid encoding p25 under an inducible Tetracycline (Tet) on/Tet off system wherein said mouse exhibits the pathological features associated with progressive neurodegeneration and the transgenic mouse exhibits behavioral symptoms of Alzheimer's disease. The specification teaches a transgenic mouse overexpressing human p25 under the Tet on/Tet off expression system in the postnatal forebrain, wherein said Tg mouse exhibits many of the biochemical and cellular aspects of AD neuropathology (specification p 65). Transgenic mice, for example, induced for 8 or 12 weeks exhibited a 25% or 40% decrease in cortical neuronal density, respectively indicating that neuropathology observed in p25 transgenic mice was due to degeneration in adulthood caused by postnatal p25 induction and was not attributed to minimal p25 expression prior to induction (specification p 65). However, the specification does not teach the creation of a transgenic mouse overexpressing p25 under the Tet on/Tet off expression system using

all inducible tissue specific promoters, wherein the pathological features correlate to behavioral symptoms of Alzheimer's disease. The data of the instant invention show the temporal relationship of the biochemical and cellular aspects of AD activity in the brain with neurodegenerative pathology of Tet/p25 Tg mice and not to behavioral phenotypes associated with neurodegenerative pathology. **Ahlijanian et al**, (PNAS, 97(6): 2910-2915, 2000) developed a Tg mouse overexpressing p25 whose genome comprises a nucleic acid encoding p25 operably linked to rat neuron-specific enolase (NSE) promoter (p 2910, 2nd column, under production of the p25 transgenic mouse section). The robust tau phosphorylation phenotypes seen and claimed for the present mouse were not seen using the NSE promoter use by Ahlijanian. Ahlijanian et al, teaches that using the NSE promoter there were no differences in the amount of phosphor- and dephospho-Ser 202, Thr-205 tau (p 2912, 2nd column, under Tau and neurofilament immunoblots) as seen in the presently claimed mouse (specification p 69, 2nd paragraph and Table 4). The phenotypes of the presently claimed mouse are therefore, dependent on the Tet on/Tet off inducible system. The specification states that other promoters can be used to produce the claimed mouse (specification p 36 last paragraph). However, the art does not provide guidance on a combination inducible promoter- DNA sequences encoding an inducer of the promoter, for example, metallothionein is an inducible promoter, but metals induce the promoter not a protein encoded by the DNA sequences. Given the unpredictability in the inducible overexpression of p25 in a Tg mouse resulting in one or more behavioral phenotypes of AD, particularly when taken with the lack of guidance and/or working examples in the

specification correlating neurodegenerative pathologic phenotypes of the transgenic mouse to be to the tetracycline response element under all tissue specific promoters, it would have required undue experimentation to predict the results achieved in a mouse comprising and expressing instant gene and the consequences of that product, and therefore, the resulting AD behavioral phenotype(s).

The art at the time of filing teaches the extent of AD phenotypes associated with p25 overexpression is directly dependent upon the promoter regulating expression of the transgene. The specification does not provide any teachings, specific guidance, or working examples for overcoming the limitations for the production of said Tg mouse raised by the state of the art. Therefore, the skilled artisan would conclude that the production of p25 Tg mouse as claimed is not enabled as broadly claimed. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention for the creation of a transgenic mouse overexpressing in the brain or forebrain a nucleic acid encoding p25 under an inducible Tetracycline (Tet) on/Tet off system wherein said mouse exhibits the pathological features associated with progressive neurodegeneration and the transgenic mouse exhibits behavioral symptoms of Alzheimer's disease without a reasonable expectation of success for the breadth of the claims.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the creation of a Tg mouse having AD behavioral phenotype using all tissue specific promoters under the inducible Tet on/Tet off system, the lack of direction or guidance provided by the specification for the creation of a Tg

mouse having AD behavioral phenotype using all tissue specific promoters under the inducible Tet on/Tet off system, the absence of working examples that correlate to the creation of a Tg mouse having AD behavioral phenotype using all tissue specific promoters under the inducible Tet on/Tet off system, the unpredictable state of the art with respect to the creation of an all tissue specific promoter Tet on/Tet off system, the undeveloped state of the art pertaining to the creation of a Tg mouse having AD behavioral phenotype using all tissue specific promoters under the inducible Tet on/Tet off system, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 73-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mayford et al, (Science, 24: 1678-1683, 1996) and Ahlijanian et al, (PNAS, 97(6): 2910-1915, 2000) in view of Lucas et al, (The EMBO Journal, 20(1 & 2): 27-39, 2001).

Mayford et al, teaches an inducible Tetracycline (Tet) Tet on/Tet off system transgenic mouse overexpressing CaMKII transgene (p 1678-1682). Mayford et al, teaches that a combination of tissue specific forebrain promoter with the Tet on/Tet off

system was used to achieve both regional and temporal control of transgene expression (abstract). Mayford does not teach an inducible Tet on/Tet off transgenic mouse overexpressing p25 resulting in the behavioral phenotypes associated with neurodegenerative pathology.

Ahlijanian et al, teaches the creation of a transgenic mouse overexpressing human p25 (p 2920-2915). Ahlijanian et al, teaches that transgenic mice developed histopathological changes localized predominantly in the amygdale, thalamus/hypothalamus and cortex and in addition said mice displayed increased spontaneous locomotor activity and differences from the control in the elevated plus-maze test (abstract and figures 2-7). Ahlijanian et al, notes that the p25 transgenic mice spent increased time on the open arms of the maze, consistent with decreased anxiety but the number of arm entries was not different, suggesting that the result is probably not due the observed increased in locomotor activity (p 2914, 2nd column). Ahlijanian et al, also suggests that the p25 transgenic mouse will facilitate the study of the sequalae of augmented cdk5 activity and hyperphosphorylated tau (downsrtream effects) (p 2915, 2nd column). Thus, Ahlijanian et al, teaches a transgenic mouse overexpressing p25 associated with AD phenotypes (p 2912, columns 1-2 and p 2913, 1st paragraph).

However, at the time of the claimed invention was made, Lucas et al, teaches the use of a tet-regulated system for the creation of Tet/Glycogen synthase kinase-3β (GSK-3β) transgenic mice wherein Tg mice overexpress GSK-3β driven by the CaMKII promoter in the cortex and hippocampus and it is associated with neurodegenerative phenotypes (p 28-37). Lucas et al, also suggested that toxicity of GSK-3β

overexpression during embryonic and postnatal development of the CNS may explain why others were unable to generate transgenic mice with detectable overexpression of the GSK-3β even with neuronal-specific promoters which led to the use of tightly controlled inducible expression systems for the creation of GSK-3β transgenic mice (p 36, 1st column, 1st paragraph). As such, Lucas et al, provide sufficient motivation for one of ordinary skill in the art to apply the Mayford et al, inducible Tetracycline (Tet) Tet on/Tet off system to create a transgenic mouse overexpressing p25 taught by Ahlijanian to study temporal and spatial relationships of the p25 expression and its association with neurodegenerative pathology and AD phenotypes.

Accordingly, in view of the teachings of Ahlijanian et al taken with the teachings of Lucas et al, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made to modify the Tet on/Tet off system of Mayford et al, by using the p25 transgenic mouse technology to monitor spatial and temporal elevations of the p25 levels under tightly controlled inducible expression systems and study the associated neurodegerative pathology and behavioral phenotypes with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make such a modification as it was recognized by Ahlijanian et al, and Lucas et al, the need to determine the spatial and temporal relationship of neurodegenaritve pathology to the behavioral phenotypes of AD.

Conclusion

4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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